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⑤4光学活性ベンジルアルコール誘導体の製法

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発明の名称

光学活性ベンジルアルコール誘導体の製法

特許請求の範囲

光学活性4—ヒドロキシフェニルグリシンをホルミル化して光学活性N—ホルミル—4—ヒドロキシフェニルグリシンを得．次いでこの化合物のフェノール性水酸基をベンジル化し．得られる光学活性N—ホルミル—4—ベンジルオキシフェニルグリシンとN—ベンジル—3.4—ジメトキシフェネチルアミンとを縮合反応させて光学活性N—ホルミル—N'—ベンジル—N'—(3.4—ジメトキシフェネチル)—4—ベンジルオキシフェニルグリシンアミドを得．この化合物を部分加水分解反応に付して光学活性N'—ベンジル—N'—(3.4—ジメトキシフェネチル)—4—ベンジルオキシフェニルグリシンアミドとなし．次いでこの化合物を酢酸中でジアゾ化反応に付し．得られる光学活性N—ベンジル—N—(3.4—ジメトキシフェネチル)—O—アセチル—4—ベンジルオキシマンデル酸アミドを還元反応に付して光学活性α—(N—ベンジル—3.4—ジメトキシフェネチルアミノメチル)—4—ベンジルオキシベンジルアルコールを得．この化合物を接触還元反応に付すことを特徴とする光学活性α—(3.4—ジメトキシフェネチルアミノメチル)—4—ヒドロキシベンジルアルコールの製法．

発明の詳細な説明

本発明は強力な持続性強心作用を有する光学活性α—(3.4—ジメトキシフェネチルアミノメチル)—4—ヒドロキシベンジルアルコールの新規製法に関する．

本発明によれば．光学活性α—(3.4—ジメトキシフェネチルアミノメチル)—4—ヒドロキシベンジルアルコール〔I〕は．光学活性4—ヒドロキシフェニルグリシン〔II〕を出発原料とし．これをホルミル化して光学活性N—ホルミル—4—ヒドロキシフェニルグリシン〔III〕を得．次いでこの化合物のフェノール性水酸基をベンジル化し．得られる光学活性N—ホルミル—4—ベンジルオキ

シフェニルグリシン〔Ⅳ〕とN－ベンジル－3.4－ジメトキシフェネチルアミン〔Ⅴ〕とを縮合反応させて光学活性N－ホルミル－N'－ベンジル－N'－（3.4－ジメトキシフェネチル）－4－ベンジルオキシフェニルグリシンアミド〔Ⅵ〕を得．この化合物を部分加水分解反応に付して光学活性N'－ベンジル－N'－（3.4－ジメトキシフェネチル）－4－ベンジルオキシフェニルグリシンアミド〔Ⅶ〕となし．次いでこの化合物を酢酸中でジアゾ化反応に付し．得られる光学活性N－ベンジル－N－（3.4－ジメトキシフェネチル）－O－アセチル－4－ベンジルオキシマンデル酸アミド〔Ⅷ〕を還元反応に付して光学活性α－（N－ベンジル－3.4－ジメトキシフェネチルアミノメチル）－4－ベンジルオキシベンジルアルコール〔Ⅸ〕を得．次いでこの化合物を接触還元反応に付すことにより．目的化合物〔Ⅰ〕を得ることができる．

以下．本発明方法を詳しく説明する．

第一工程のホルミル化反応は．原料化合物〔Ⅱ〕とホルミル化剤とを溶媒の存在下もしくは非存在下に反応させることにより実施できる．ホルミル化剤としては．たとえばギ酸と酢酸との混合無水物などが適当である．反応は冷時乃至室温にてスムースに進行し．高収率にて化合物〔Ⅲ〕を得る．

第二工程のベンジル化反応は．適当な溶媒中で化合物〔Ⅲ〕とベンジル化剤とを反応させることにより実施できる．ベンジル化剤の例としては．たとえばベンジルクロリド．ベンジルブロミド等をあげることができる．反応系に炭酸カリウム等の脱酸剤を存在させれば反応を促進するので好都合である．反応は熱時好適に進行し．好収率にて化合物〔Ⅳ〕を製することができる．

第三工程の縮合反応は．まず．適当な溶媒中で化合物〔Ⅳ〕を活性エステル化剤と反応させて化合物〔Ⅳ〕の活性エステルを得．ついでこのエステルとアミン〔Ⅴ〕とを反応させることにより実施するのが好ましい．活性エステル化剤としては．たとえばイソブチルクロロカーボネート等があげられる．反応は冷却下に．特に好ましくは約－30℃にてスムースに進行し．好収率にて化合物〔Ⅵ〕を

得ることができる．

第四工程の部分加水分解反応は．この種の反応の常法に従い．例えば適当な溶媒中で化合物〔Ⅵ〕と塩化水素を20%含有するメタノールとを接触処理することにより実施できる．反応は室温にても好適に進行し．化合物〔Ⅶ〕を高収率にて得る．

第五工程のジアゾ化反応は．酢酸中で化合物〔Ⅶ〕と亜硝酸とを反応させることにより実施できる．亜硝酸は．たとえば反応容器中で亜硝酸ソーダと酢酸とを反応させて製し．直ちに使用するのが好ましい．反応は室温下にてもスムースに進行する．更に．このジアゾ化に随伴してアセトキシ化が生起し．一挙に化合物〔Ⅷ〕を得ることができる．尚．本工程では一部ラセミ化が生起している．

第六工程の還元反応は．適当な溶媒中で化合物〔Ⅷ〕を還元剤で還元することにより実施できる．還元剤としては．たとえばリチウムアルミニウムヒドリド．アラン．ジボラン等が使用できる．反応は熱時好適に進行し．化合物〔Ⅸ〕を製することができる．

最終工程の接触還元反応は．この種の反応の常法に従い．適当な溶媒中で接触還元触媒の存在下に化合物〔Ⅸ〕と水素ガスとを接触させることにより実施できる．前記触媒としては例えばパラジウム・カーボン．酸化白金等があげられる．反応は常温常圧乃至加温加圧下にスムースに進行し．目的化合物〔Ⅰ〕を得ることができる．

実施例

(1) D－4－ヒドロキシフェニルグリシン50 g．ギ酸200 ml及び無水酢酸80 mlの溶液を13～15℃にて15時間．次いで室温にて1夜かくはんする．反応混合物を減圧濃縮し．残査にエーテルを加え．析出物を口取し．エーテルで洗浄すれば．粗製のD－N－ホルミル－4－ヒドロキシフェニルグリシンを51 g得る．収率87.4%．

本品をイソプロパノールで再結晶すれば．mp. 183～185℃（分解）を示す．

$[\alpha]_D^{20}$ −260°（C＝0.937．メタノール）

(2) 本品10 g．ベンジルクロリド10 g．炭酸カリウム14.2 g及びメタノール170 mlの混合物を約

チルアミノメチル）－4－ヒドロキシベンジルアルコールを1.2g得る。

本品はメタノールより2回再結晶を行えばmp. 151～155℃を示すプリズム晶となる。

$[\alpha]_D^{27}$ － 4.15°（C＝1，メタノール）

Mass$^{m}/_{e}$ ： 317（M^+）

本品の光学純度は15％である。

〔ℓ－α－（3.4－ジメトキシフェネチルアミノメチル）－4－ヒドロキシベンジルアルコールの純品は，mp. 166℃（分解）にして，$[\alpha]_D^{20}$ － 28°（C＝1，メタノール）を示す。〕

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SPECIFICATION

Title of the Invention

PRODUCTION METHOD OF OPTICALLY ACTIVE BENZYL ALCOHOL DERIVATIVES

Claim

A method for producing optically active α-(3,4-dimethoxyphenethylaminomethyl)-4-hydroxybenzyl alcohol, wherein:

optically active 4-hydroxyphenylglycine is formylated to obtain optically active N-formyl-4-hydroxyphenylglycine;

the phenolic hydroxyl group of the obtained compound is benzylated;

the obtained optically active N-formyl-4-benzyloxyphenylglycine and N-benzyl-3,4-dimethoxyphenethylamine are condensed to obtain optically active N-formyl-N'-benzyl-N'-(3,4-dimethoxphenethyl)-4-benzyloxyphenylglycineamide;

the obtained compound is subjected to partial hydrolyzation to give optically active N'-benzyl-N'-(3,4-dimethoxyphenethyl)-4-benzyloxyphenylglycineamide;

the obtained compound is subjected to diazotization in acetic acid;

obtained optically active N-benzyl-N-(3,4-dimethoxyphenethyl)-O-acetyl-4-benzyloxy mandelic acid amide

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is reduced to obtain optically active α-(N-benzyl-3,4-dimethoxyphenethylaminomethyl)-4-benzyloxybenzyl alcohol; and

the obtained compound is subjected to catalytic reduction.

Detailed Description of the Invention

The present invention relates to a novel method for producing optically active α-(3,4-dimethoxyphenethylaminomethyl)-4-hydroxybenzyl alcohol, which has powerful and long-lasting cardiotonic action.

According to the present invention, the optically active α-(3,4-dimethoxyphenethylaminomethyl)-4-hydroxybenzyl alcohol [I] is obtained as follows. Optically active 4-hydroxyphenylglycine [II] is used as a starting material and is formylated to obtain optically active N-formyl-4-hydroxyphenylglycine [III]. Then, the phenolic hydroxyl group of the compound is benzylated. The obtained optically active N-formyl-4-benzyloxyphenylglycine [IV] and N-benzyl-3,4-dimethoxyphenethylamine [V] are condensed to obtain optically active N-formyl-N'-benzyl-N'-(3,4-dimethoxphenethyl)-4-benzyloxyphenylglycineamide [VI]. The compound is subjected to partial hydrolyzation to give optically active N'-benzyl-N'-(3,4-dimethoxyphenethyl)-4-benzyloxyphenylglycineamide [VII]. Next, the compound is subjected to diazotization in acetic acid. The obtained optically active N-benzyl-N-(3,4-dimethoxyphenethyl)-O-acetyl-4-benzyloxy mandelic acid amide [VIII] is reduced to obtain optically active α-(N-benzyl-3,4-dimethoxyphenethylaminomethyl)-4-benzyloxybenzyl alcohol [IX]. Then, the obtained compound is subjected to catalytic reduction. Thus, the target compound [1] can be obtained.

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Hereinafter, the method of the present invention will be described in detail.

Formylation in the first step can be performed by reacting the starting compound [II] with a formylating agent in the presence or the absence of a solvent. A suitable formylating agent may be, for example, a mixed-acid anhydride of formic acid and acetic acid. The reaction proceeds smoothly at room temperature or below. Thus, compound [III] is obtained in a high yield.

Benzylation in the second step can be performed by reacting compound III with a benzylating agent in a suitable solvent. The benzylating agent may be, for example, benzyl chloride, benzyl bromide or the like. The presence of a deacidifying agent such as potassium carbonate in reaction system is preferable because the reaction can be accelerated. The reaction proceeds best when heated. Thus, compound [IV] is produced in a high yield.

Condensation in the third step is preferably performed by first reacting compound [IV] with an active esterifying agent in a suitable solvent to obtain an active ester of compound [IV] and then reacting the ester with amine [V]. The active esterifying agent may be, for example, isobutyl chlorocarbonate or the like. The reaction proceeds smoothly when cooled, preferably at about -30°C. Thus, compound [VI] is obtained in a high yield.

Partial hydrolyzation in the fourth step can be performed in accordance with the usual method of such a reaction, for example, by contacting compound [VI] with methanol containing 20% hydrogen chloride in a suitable solvent. The reaction proceeds best even at room

temperature. Thus, compound [VII] is obtained in a high yield.

Diazotization in the fifth step can be performed by reacting compound [VII] with nitrous acid in acetic acid. It is preferable to produce a nitrous acid by reacting sodium nitrite with acetic acid in a reaction container, for example, and using it immediately. The reaction proceeds smoothly at room temperature. With this diazotization, acetoxylation occurs and compound [VIII] can be obtained at once. In this method, racemization partially occurs.

Reduction in the sixth step can be performed by reducing the compound [VIII] with a reducing agent in a suitable solvent. As the reducing agent, for example, lithium aluminum hydride, alane, diborane or the like may be used. The reaction proceeds best when heated. Thus, compound [IX] can be produced.

Catalytic reduction in the final step can be performed by contacting compound [IX] with hydrogen gas in the presence of a catalytic reduction catalyst in a suitable solvent in accordance with the usual method of such a reaction. The catalyst may be, for example, palladium carbon, platinum oxide or the like. The reaction smoothly proceeds from ambient temperature and atmospheric pressure to warmed temperature and high pressure. Thus, target compound [I] can be obtained.

Examples

(1) A solution of 50 g of D-4-hydroxyphenylglycine, 200 ml of formic acid, and 80 ml of acetic anhydride was stirred at 13-15°C for 15 hours, and then was stirred at

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room temperature overnight. The reaction mixture was concentrated at reduced pressure. Ether was added to the residue. The precipitate was filtered and washed with ether to obtain 51 g of crude D-N-formyl-4-hydroxyphenylglycine. The yield was 87.4%.

The product exhibits mp. 183-185°C (decomposition) after recrystallization with isopropanol.

$[\alpha]_D^{20}$ −260° (C = 0.937, methanol)

(2) A mixture of 10 g of the above product, 10 g of benzyl chloride, 14.2 g of potassium carbonate, and 170 ml of methanol was stirred under reflux for 6 hours. After the reaction, methanol was evaporated at reduced pressure. Water was added to the residue and the solution was acidified with acetic acid. The precipitated crystals were filtered, washed with water, and then dried to obtain 12.1 g of D-N-formyl-4-benzyloxyphenylglycine as white crystals. The yield was 82.9%.

The product exhibits mp. 180-182°C (decomposition) after recrystallization with ethanol.

$[\alpha]_D^{20}$ − 196.5° (C = 0.85, methanol)
IR ν_{max}^{Nujol} (cm^{-1}): 3400, 1700, 1630
Elemental analysis: $C_{16}H_{15}O_4N$
Calculated.: C, 67.36 ; H, 5.30 ; N, 4.91
Experimental Value: C, 67.31 ; H, 5.42 ; N, 4.83

(3) A mixed solution of 2.1 g of the above product, 0.75 g of N-methylmorpholine, and 30 ml of tetrahydrofuran (hereinafter, referred to as THF) was cooled to -50°C. 5 ml of a THF solution of 1 g of isobutyl chlorocarbonate was dropped thereinto and stirred at the same temperature for 30

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minutes. 5 ml of a THF solution of 2 g of N-benzyl-3,4-dimetoxyphenethylamine was dropped into this solution at -30°C. After the addition was completed, refrigeration was stopped, and stirring was continued until the reactant reached room temperature to finish the reaction. The reaction mixture was injected into water and extracted with ethyl acetate. The extracted layer was washed with water and dried, and then the solvent was evaporated. The oil of residue (3.79 g) was purified by silica gel chromatography and 2.96 g of D-N-formyl-N'-benzyl-N'-(3,4-dimethoxyphenethyl)-4-benzyloxyphenylglycineamide was obtained as an oil. The yield was 74.4%.

$[\alpha]_D^{27}$ - 31.7° (C = 1.0, methanol)
IR ν_{max}^{liq} (cm^{-1}) : 3300, 1670, 1640

(4) 10 ml of methanol containing hydrogen chloride by 20% was added to 30 ml of methanol solution of 2.7 g of the above product and stirred at room temperature for 3 hours. After the reaction, methanol was evaporated at reduced pressure, and the residue was dissolved in water. This aqueous solution was basified with sodium bicarbonate and extracted with ethyl acetate. The extracted layer was washed with water and dried, and then the solvent was evaporated. The oil of residue (2.35 g) was purified by alumina column chromatography and 2.25 g of D-N'-benzyl-N'-(3,4-dimethoxyphenethyl)-4-benzyloxyphenylglycineamide was obtained as oil. The yield was 87.9%.

$[\alpha]_D^{27}$ + 26.2° (C = 0.93, methanol)
IR ν_{max}^{liq} (cm^{-1}) : 3380, 3300, 1640

(5) 0.8 g of sodium nitrite was added to 30 ml of acetic acid solution of 4.6 g of the above product at a temperature of 17-20°C, little by little (over about 1 hour and 20 minutes). Further, after stirring for 2 hours,

acetic acid was evaporated at reduced pressure. The residue was provided with water and extracted with ethyl acetate. The extracted layer was sequentially washed with dilute hydrochloric acid, sodium bicarbonate solution, and a salt solution, and then dried. The solvent was evaporated and the oil of the residue (4.67 g) was separated by silica gel column chromatography. 3.34 g of N-benzyl-N-(3,4-dimetoxyphenethyl)-O-acetyl-4-benzyloxy mandelic acid amide was obtained as an oil. The yield was 66.8 g.

$(\alpha)_D^{20} - 1.6°$ (C = 1.14, methanol)
IR ν_{max}^{liq} (cm^{-1}) : 1740, 1660
Mass %: 553 (M^+)

(6) 10 ml of THF solution of 0.66g of the above product was slowly dropped into 20 ml of a mixture of 150 mg of lithium aluminum hydride under a nitrogen stream, and then the resultant was stirred under reflux overnight. The reactant was provided with 0.1 ml of a 15% caustic soda aqueous solution and 0.3 ml of water, and stirred for a while. Insoluble residue was filtered out. The solvent was evaporated at reduced pressure from the filtrate. The oil of the residue (0.59 g) was purified by silica gel column chromatography to obtain 0.5 g of α-(N-benzyl-3,4-dimethoxyphenethylaminomethyl)-4-benzyloxybenzyl alcohol as an oil. The yield was 84.7%.

IR ν_{max}^{liq} (cm^{-1}) : 3450
Mass %: 497 (M^+)

(7) A mixture of 2.7 g of the above product, 0.5 g of 10% palladium carbon, 1 ml of 10% hydrochloric acid and 40 ml of ethanol was shaken at an ambient temperature and atmospheric pressure under a hydrogen stream. After absorption of a calculated amount of hydrogen, the catalyst was filtered out and the filtrate was concentrated at

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reduced pressure. The residue was dissolved in dilute hydrochloric acid. The water layer was washed with chloroform, basified with ammonia water, and extracted with chloroform. The extracted layer was dried, and then the solvent was evaporated. The mixed solution of isopropanol and isopropyl ether was added to oil of the residue (1.47 g). The precipitated crystal was filtered to obtain 1.2 g of l-α-(3,4-dimethoxyphenethylaminomethyl)-4-hydroxybenzyl alcohol.

The product is prism crystals exhibiting mp. of 151-155°C after two-time recrystallization from methanol.

$[\alpha]_D^{27} - 4.15°$ (C = 1 . methanol)
Mass %: 317 (M^+)

The optical purity of the product is 15%.

[The pure product of l-α-(3,4-dimethoxyphenethylaminomethyl)-4-hydroxybenzyl alcohol exhibits mp. 166°C (decomposition) and $[\alpha]_D^{20}$-28° (C=1, methanol).]